

patenting as being obvious over claims 1, 2, 4-7, 12-13, and 15-19 of U.S. Pat. No. 5,952,176 (hereinafter referred to as "U.S. '176") in view of Chirikjian et al., U.S. Pat. No. 5,656,430 (hereinafter referred to as "U.S. '430"). Claims 1-2 and 8-23 have been further rejected under 35 U.S.C. §103 as being obvious over WO 97/03210 (the PCT International Publication corresponding to the U.S. '176 patent, hereinafter referred to as WO '210) combined with U.S. '430. Applicants traverse these rejections and withdrawal thereof is respectfully requested.

In response to Applicant's arguments of July 5, 2002, the Examiner asserts that,

Although McCarthy et al. do not specifically disclose cleaving the DNA at the abasic site, McCarthy et al. disclose cleaving phosphate linkage at abasic sites and [then] sic analyzing the cleavage products (See column 73, claim 1) in which the method steps encompass "cleaving the DNA at the abasic site."

Applicants respectfully submit that the Examiner's interpretation of the disclosure of the McCarthy et al. references (U.S. '176 and its PCT counterpart, WO '210) is incorrect.

There is no disclosure, either explicitly or inherently, in the McCarthy et al. references of cleavage at abasic sites, which results in a 3' hydroxyl terminus on the upstream fragment, whereby an extendible upstream fragment is generated.

The generation of 3' hydroxyl termini is a novel feature of the invention, as is the fact that they are extendible. As noted above, there is no disclosure of these features in McCarthy et al. In fact, while on the one hand the Examiner suggests that McCarthy et al. may contain such a disclosure, the Examiner herself later clearly states,

Furthermore, although McCarthy et al. do not disclose generating an extendible DNA fragment having a 3' hydroxyl terminus in which a template nucleic acid has partial or full sequence complementarity to the upstream fragment and analyzing the resulting fragment....

Thus, contrary to the assertion of the Examiner discussed on page 2 of the present response, McCarthy et al. does not disclose or suggest key recited elements of the present invention. Applicants request that the Examiner reconsider the disclosures of McCarthy et al. in view of what the references reasonably may be asserted to teach. The deficiencies of the McCarthy et al. references are not compensated for by Chirikjian et al. and as such the invention is not achieved if the references are combined.

The Examiner asserts that Chirikjian et al. disclose that the glycosylase generates an abasic site at a point of mismatch, which is subsequently cleaved by an endonuclease. See Item 4, page 3 of the Advisory Action. The Examiner further asserts that this disclosure in Chirikjian et al. suggests the feature of step ii) of claim 1. However, the Examiner has provided no scientific or

evidence

logical evidence for this leap of interpretation. Excision of a base by a glycosylase at a site of a mismatch is a fundamentally different event to excising a modified base by a glycosylase that does not recognize a mismatch *per se*. This feature actually reflects one of the advantages of the present invention, which is that the present invention is independent of mismatch formation. Because of the independence from the formation of mismatches, the homozygotic nature of a sample for a specific polymorphism can be directly determined. Detection of this type of polymorphism can at best only be partially inferred using the method of Chirikjian et al.

In addition, the "probe" in Chirikjian et al. is a piece of synthetic nucleic acid and it is this piece of synthetic nucleic acid that is extended. In the invention, it is the cleaved product, i.e. the upstream fragment that is derived from the amplification of the DNA and incorporation of the modified nucleotides that is extended and not the artificial oligonucleotide/template that is subsequently added. Thus, for several reasons it is not possible to achieve the present invention, or the advantages thereof, from the combined teachings of the McCarthy et al. references and Chirikjian et al. Withdrawal of the rejections is therefore respectfully requested.

2) Claims 3-7 further remain rejected as being obvious over WO '210 combined with U.S. '430 and Dianov et al. In the Advisory Action, the Examiner asserts, in part, that Dianov et al. teaches the features of present claims 3-7.

Applicants again note that Dianov et al. fails to compensate for the failings of the primary references WO '210 combined with U.S. '430. As such, it is not possible to achieve the invention by combining Dianov et al. with WO '210 and U.S. '430.

Dianov et al. describes a method of determining the repair gap in DNA following action by DNA glycosylases and endonucleases to repair damaged DNA. The process described in Dianov et al. demonstrates the insertion of 1-2 nucleotides and the closing of the gap in the DNA. The process of Dianov et al. necessarily requires the incorporation of 1-2 nucleotides by polymerase action of a downstream processing dRpase or exonuclease activity, which is not required by the present invention. The present invention, on the other hand, involves the extension of the upstream fragment, i.e. the released extendible upstream DNA fragment, in the presence of an enzyme that allows for such extension and which may be a polymerase or a ligase, to a length determined by the

additional/new template used to drive the reaction and/or the nucleotides supplied for the reaction.

A further difference in the present invention and the references lies in the fact that Dianov et al. only disclose cleavage on the 5' side, followed by action of 5' dRpase or 5' to 3' exonuclease. The present method, on the other hand, involves the cleavage of the DNA at the abasic site following excision of the modified base. In the present method, cleavage can be either on the 3' or the 5' side of the abasic site. Cleavage on the 3' side of the abasic site is followed by the subsequent cleavage of the 3' dRp moiety on the upstream fragment to generate a 3' OH group, if necessary. See claim 5.

Thus, it is not possible to achieve the present invention from the teachings of Dianov et al., WO '210 and U.S. '430. As such, the invention of claims 3-6 is not obvious over the cited references and withdrawal of the rejection is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, PhD (Reg. No. 40,069) at the telephone number of the listed below.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a two (2) month extension of time for

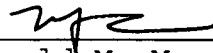
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filing a reply in connection with the present application, and the required fee is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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